

### **Remarks**

Claims 1, 3-6, 8-10, 12-14, 16-17, and 19-28 are pending. Claims 1 and 20-21 are amended to correct format. Claims 20 and 21 are amended herein to clarify the steps in the claimed methods.

No new matter is added herein. Applicants respectfully request reconsideration of the application based on the foregoing amendments and the following remarks.

### ***Rejections under 35 U.S.C. § 103***

Claims 1, 3-6, 8-10, 12-14, 16-17, and 19-28 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Nakatani et al (US Patent No. 5,886,152), in view of Vincenti et al (New Eng. J. Med, 1998, Vol. 338, p. 161-165) in view of Hayoshi and Swanborg (J. Immunol. 1987, Vol. 138, p. 3771-3775), and further in view of Paty et al. and Jacobs et al. Applicants respectfully disagree with this rejection.

Nakatani et al. disclose a humanized monoclonal antibody B-B10, which includes specified complementarity determining regions (see SEQ ID NOs: 1-6). Nakatani et al. disclose that this antibody is of use to treat any tumors, T-cell dependent allergy or autoimmune diseases. As examples of T cell-dependent allergy and autoimmune disease, Nakatani et al. list "myocarditis, diabetes mellitus, myasthenia gravis, lupus erythematosus, Crohn disease, multiple sclerosis, AIDS, Meningitis, Arthritis." Nakatani et al. do not disclose the combination of humanized B-B10 with any other cytokines, let alone with interferon-beta.

Vincenti et al. disclose the use of daclizumab to prevent acute rejection of renal transplantation. Specifically, Vincenti et al. that treatment of patients with daclizumab prior to transplantation, and once every other week (along with cyclosporine, azathioprine and prednisone) after transplantation, for a total of five doses, reduced the rate of acute rejection in kidney transplant recipients. However, administration of daclizumab did not result in a significant effect on kidney graft survival at twelve months. Vincenti et al. do not disclose the use of any cytokines, let alone the use of interferon-beta.

Hayoshi and Swanborg disclose that a monoclonal antibody to rat IL-2 receptor, OX39 inhibits the activation of effector cells in experimental allergic encephalomyelitis (EAE). Hayoshi and Swanborg disclose that OX39 is an anti-Tac antibody. However, Hayoshi and Swanborg disclose that OX39 only inhibited EAE effector cell activation when added to cultures at time zero or 24 hours, but did not have any effect on effect on cell activation at 48 hours.

Hayoshi and Swanborg state that “it will be important to ascertain whether OX39 can suppress EAE in immunized rats” (see page 3775). Thus, at best, Hayoshi and Swanborg make it obvious to try to test anti-Tac antibodies in a rat model of multiple sclerosis. However, Hayoshi and Swanborg do not suggest any specific antibodies that could be experimentally tested. Moreover, Hayoshi and Swanborg do not disclose the administration of OX39 with other cytokines, let alone interferon beta.

Paty et al. describes the administration of interferon-1 beta-1b to patients with multiple sclerosis. Paty et al. do not suggest, or render obvious, the use of any additional agents with interferon-1 beta-b for the treatment of multiple sclerosis, let alone the use of a monoclonal antibody such as daclizumab.

Jacobs et al. teaches the administration of interferon-1 beta-1a to patients with multiple sclerosis. Jacobs et al. do not suggest, nor render obvious the use of any additional agents with interferon-1 beta-1a for the treatment of multiple sclerosis, let alone the use of a monoclonal antibody such as daclizumab.

*1. There is no incentive to combine Vincenti et al. with the other cited prior art*

Vincenti et al. is a publication describing the effect of daclizumab on transplant rejection. Specifically, daclizumab was administered in conjunction with therapy with cyclosporine, azathioprine and prednisone. The addition of daclizumab to therapy with cyclosporine, azathioprine and prednisone reduced the frequency of short term acute rejection. However, the addition of daclizumab did not significantly affect long term survival of kidney grafts. An immune response to a heterologous graft is very different from an autoimmune response, and different therapeutic regimens are used in treatment. As stated in the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Courts Decision in *KSR International Co. v. Teleflex Inc.* (Federal Register vol. 72, No. 195, pages 57526-57535, hereinafter “the Examination Guidelines”) known work in one field of endeavor may prompt variations in it for use in a different field based on design incentives or market forces. In the present case, there simply are no incentives to for one of skill in the art to apply a therapy used to prevent acute (but not chronic) transplant rejection to the treatment of a chronic condition, let alone an autoimmune disease such as multiple sclerosis. In addition, the Guidelines indicate that there must be some teaching, suggestion or motivation *in the prior art itself* that would lead one to modify the prior art reference or to combine teachings. There simply is no teaching in

Vincenti et al. to use treatments for transplant rejection in conjunction with treatments for multiple sclerosis. Similarly, there is no mention of transplant rejection in any of Nakatani et al., Hayoshi and Swanborg, Paty et al. or Jacobs et al. to use compounds effective for the treatment of multiple sclerosis for the treatment of transplant recipients.

*2. The claimed methods are unpredictable in view of the cited prior art*

The Office action states that there is motivation to combine Nakatani et al. (which teaches the use of human monoclonal antibody B-B10 to treat autoimmune diseases) and Hayoshi and Swanborg (which teach the use of OX39 to treat EAE in rats) with the teachings of Paty et al. and Jacobs et al. However, even if one were to make this combination (and the Applicants do not concede that the combination would be made), one of skill in the art would only arrive at using humanized B-B10, or perhaps human OX39 in combination with interferon-beta. As Nakatani et al. and Hayoshi and Swanborg teach the effectiveness of B-B10 and OX39, respectively, there simply is no motivation to substitute any other antibody. Moreover, even if a variation were made to use another antibody that specifically bound the IL-2 receptor, the effectiveness of this therapy would not be predictable.

The review process required for FDA approval speaks to the lack of predictability as to whether an antibody will be effective for therapy in humans. As noted in Exhibit A (printout of an article from the National Cancer Institute entitled "Understanding the Approval Process for New Cancer Treatments: The FDA's Role," posted December 30, 1999), the FDA estimates that it takes about 8.5 years to study and test any new drug (including antibodies) before it can be approved for human use. If a treatment is promising in the laboratory then an Applicant can apply to test the treatment in humans. For each monoclonal antibody of potential use as a therapeutic agent, Applicants must submit an Investigational New Drug (IND) application. If the treatment makes it through the clinical trials process, then a New Drug Application can be submitted. This application is limited to the EXACT chemical or drug produced by a specific process. Thus, clearly the FDA (along with those of skill in the art) views each antibody as unique, and each drug combination as unique. Thus, one of skill in the art would not view the claimed methods, directed to the combined use of daclizumab and interferon-beta as being obvious over (1) a description of methods that use another monoclonal antibody individually; (2) methods that use interferon-beta individually; or even (2) methods that use a monoclonal antibody for a completely different disease process. Thus, the claimed methods are clearly non-

obvious over Nakatani et al. and Hayoshi and Swanborg, even in view of Paty et al. and Jacobs et al., and further in view of Vincenti et al.

*3. Therapeutic agents effective individually for a treatment do not render obvious the use of a combination of agents*

The Office action alleges that if two treatments are individually effective for the treatment of disease, it is obvious to combine these two treatments, and that the optimization of dosing is simply routine. Applicants respectfully disagree with these assertions.

Applicants submit that a combination of agents, each separately effective for the treatment of a specific disease, does not ensure a beneficial result when the agents are administered in combination. This is evidenced by Bowman et al. (Transplantation, 53: 556-9, 1992, of record). Treatment of renal transplant recipients with low-dose cyclosporine, azathioprine and prednisone (triple therapy) results in an increase in acute rejection episodes as compared to treatment with cyclosporine and prednisone (double-therapy). Triple therapy of renal transplant recipients also led to an increased infection rate as compared to double therapy. The addition of an agent (azathioprine) resulted in more acute rejection episodes, greater immunosuppression requirements, and a resultant increase in infections. Thus, the use of a combination of agents does not ensure a superior effect.

Agents that are of use individually for the treatment of a disease are often used at a different dose when used in a combinatorial therapeutic for the treatment of the same disease. For example, lower doses of tiazofurin and ribavirin can be used at significantly lower doses when they are used together for the treatment of experimental autoimmune encephalitis (an animal model of multiple sclerosis). In addition, a dose of a specific agent that is of use for the treatment of one disease may not be of use for treating another disease. For example, different doses of methotrexate are recommended for the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis and psoriasis.

Applicants submit that a disclosure relating to the treatment of multiple sclerosis using one type of therapy (such as interferon-beta 1b), does not necessarily suggest combination with another reference describing the treatment of multiple sclerosis using another type of therapy (OX39). In addition, even if the impermissible combination were made, one of skill in the art must reasonably expect the claimed combination to work (see *In re O'Farrell*, 853 F.2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed Cir. 1988)). A combination of multiple agents, each effective

for the treatment of the same disease, may not provide a beneficial result (see Exhibit A from the response submitted on September 19, 2007, and see the above discussion). Moreover, an agent that is of use individually for the treatment of one disorder at a specified dose may be used in a combination therapy at an entirely different dose. Even if an agent is shown to be effective for multiple diseases, the agent can be used at entirely different concentrations and/or dosing schedules for different diseases. Thus, even if one of skill in the art were to combine the teachings of Study of Nakatani et al, Hayoshi and Swanborg, Paty et al., and Jacobs et al. with Vincenti et al. (which is not a permissible combination) there is not a reasonable expectation that a dosing regimen would be effective. For example, it could not be predicted that a dosage would be effective wherein the antibody that specifically binds the interleukin-2 receptor is administered every other week for two weeks and then monthly, and/or wherein the antibody is administered at a dose of 1-2 mg/kg.

*4. The cited prior art does not teach the selection of a subject that has failed to respond to treatment with interferon-beta (Claims 20 and 21)*

As stated in the Examination Guidelines the rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art. With regard to claims 20 and 21, none of the cited references teach the selection of a subject who has failed any other therapy, let alone treatment with interferon beta. Based on the cited prior art, it simply would not be predictable that a subject who failed one form of therapy would respond to another form of therapy. Specifically, none of the references provide any information that would lead one of skill in the art to modify the therapeutic regimens to select subjects who have failed therapy.

Paty et al. and Jacob et al. both teach the effectiveness of interferon-beta for the treatment of multiple sclerosis. They simply do not suggest treatments for subjects who fail interferon beta therapy. Similarly, Hayoshi and Swanborg and Natkatani et al. teach the effectiveness of antibodies that bind the interleukin-2 receptor, but do not teach the selection of subjects that have failed any therapeutic regimen, let alone treatment with interferon-beta. Thus, the effectiveness of daclizumab in a subject who does not respond to interferon-beta is simply not a “predictable result” based on Paty et al, Jacob et al, Hayoshi and Swanborg and/or Natkatani et al.

4. *Evidence of the unexpectedly superior results overcomes a prima facie case of obviousness*

The Guidelines state that Applicants can submit argument or evidence to demonstrate that the results of the claimed combination were unexpectedly superior. As set forth in the Declaration of Dr. Alice Fong, *the reduction in the number of new lesions following treatment with daclizumab would not have been predicted based on prior results*. Dr. Alice Fong describes results obtained in a multi-center, randomized, double-blind, placebo controlled clinical trial that was performed at 51 sites, both in the U.S. and abroad. This study was designed to investigate the effect of concurrent daclizumab and interferon-beta therapy in patients with active relapsing remitting multiple sclerosis (MS). In this study, patients with multiple sclerosis (MS) were treated using one of three treatment protocols: (1) daclizumab (Roche Penzberg) at 2 mg/kg subcutaneously every two weeks with concurrent interferon-beta therapy; (2) daclizumab at 1 mg/kg subcutaneously every four weeks with concurrent interferon beta therapy (a placebo was administered every two weeks, to alternate with daclizumab); and (3) placebo every two weeks with concurrent interferon beta therapy (control group). The primary efficacy endpoint was the number of new or enlarged gadolinium contrast enhancing lesions on monthly brain MRIs between week 8 and week 24 of the study. Statistical analyses were used to study the efficacy of the treatment regimens. Individuals in Group (1), who received 2 mg/kg daclizumab every two weeks with beta interferon had a 72% reduction ( $p=0.004$ ) in the mean number of new or enlarged gadolinium contrast enhancing lesions as compared to the control group (who received only interferon-beta). Individuals in Group (2), who received 1 mg/kg daclizumab every four weeks with beta interferon had a 25% reduction ( $p=0.501$ ) in the mean number of new or enlarged gadolinium contrast enhancing lesions as compared to the control group (who received only interferon-beta). Thus, treatment with daclizumab in combination with interferon-beta provided an unexpected reduction in the number of gadolinium contrast enhancing lesions than treatment with interferon-beta alone.

The Declaration of Dr. Alice Fong was submitted on September 19, 2007. However, the Office action indicates that Dr. Fong's *curriculum vitae* and an exhibit were not received. Thus, an additional copy of Dr. Fong's Declaration, with the accompanying Exhibits A and B, and her *curriculum vitae* are submitted herewith via EFS. Applicants apologize for any inconvenience. Applicants also respectfully request that the Declaration be considered.

The finding of an unexpected result documented in the Declaration of Dr. Fong overcomes any *prima facie* case of obviousness based on Nakatani et al., Hayoshi and Swanborg, Vincenti et al., Paty et al, and/or Jacobs et al., alone or in any combination.

Reconsideration and withdrawal of the rejection of claims 1, 3-6, 8-10, 12-14, 16-17, and 19-28 under 35 U.S.C. § 103 are respectfully requested.

### ***Double Patenting***

Claim 20 remains rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-21 and 29-34 of co-pending application No. 10/607,598. Claim 20 has been amended herein to indicate that the subject is treated with a therapeutically effective amount of beta-interferon.

As discussed in the response submitted on September 19, 2007, the claims in the '859 patent are directed to the treatment of a subject with multiple sclerosis with a therapeutically effective amount of daclizumab (1) *in the absence of treatment with beta interferon, wherein (2) the subject has failed to respond to previous treatment with beta interferon.* The claims of the present application are directed to treatment of subjects with multiple sclerosis with a therapeutically effective amount of daclizumab *in combination with* therapeutically effective amount of interferon-beta.

Claim 20 as amended of the present application and the claims of the '859 patent are patentably distinct (and do not overlap in scope) with the claims of the present application. As the claims of the '859 patent recite that daclizumab must be administered *in the absence of interferon* they *teach away* from the combined use of daclizumab and interferon-beta for the treatment of multiple sclerosis.

Reconsideration and withdrawal of the rejection are respectfully requested.

### **Conclusion**

Applicants believe the present application is ready for allowance, which action is requested. If any issues remain prior to the issuance of a Notice of Allowance, applicants respectfully request that Examiner Hissong and/or Examiner Nickol contact the undersigned at the telephone number listed below. A written request for an interview was included in the response submitted on September 19, 2007. *This renewed request is submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.*

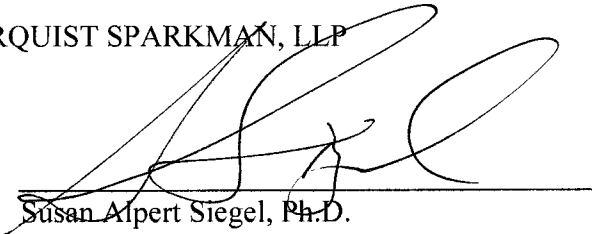
If there are any minor matters that remain to be addressed, or any documentation is missing from the patent application file, the Examiner is respectfully requested to telephone the undersigned so that prosecution can be expedited.

Respectfully submitted,

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